

REMARKS

The present invention relates to methods for the treatment of Acquired Immunodeficiency Syndrome.

Claims 42 and 46 are pending in the present application.

Withdrawn Objections and Rejections

The Examiner has indicated that the Request for Continued Examination filed on February 10, 2003 has been entered and the finality of the previous Office Action has been withdrawn. In addition, Applicants are pleased to note that the objection to the IDS, particularly the objection to Reference BU (Ohta et al., 1991, Japanese Journal of Gastroenterology 88: 209-210) has been withdrawn in view of Applicants' concise summary. Applicants are very pleased to note the Examiner's rejections referencing Uehara et al. (1993, J. Interferon Research 13: Supp), Skurkovich et al. (U.S. Patent 4,824,432), and Probert et al. (1995, Proc. Nat'l Acad. Sci. USA 92: 11294-11298) have been withdrawn.

Rejection of Claims 42 and 46 pursuant to 35 U.S.C. §112, first paragraph

The Examiner has rejected claims 42 and 46 under 35 U.S.C. §112, first paragraph for, in the Examiner's opinion, lack of enablement. Specifically, the Examiner states that the method claimed in the instant invention is not enabled because in the Examiner's view, the Example set forth in the specification is prophetic, and further because, in the Examiner's view the Example does not specify whether the administered anti-tumor necrosis factor antibody is directed against tumor necrosis factor alpha or tumor necrosis factor beta.

Applicants cite §2164.02 of the MPEP, where it states, "Compliance with the enablement requirement of 35 U.S.C. §112, first paragraph, does not turn on whether an example is disclosed. An example may be 'working' or 'prophetic'." Applicants respectfully submit that the Example set forth in the specification as filed, beginning at page 40, line 17, whether prophetic or working, satisfies the requirements of MPEP §2164.02 and 35 U.S.C. §112, first paragraph. As stated in the above-identified section of the MPEP, an example is not required, yet Applicants have provided one. Moreover, if an example is provided, it may be prophetic or working, which Applicants have also provided. Therefore, by providing an example, Applicants' specification adequately meets the enablement requirement of 35 U.S.C. §112 as construed in the

MPEP, and the present invention is therefore enabled.

In addition, the Examiner has stated that the Example set forth in the specification does not specify whether the administered anti-TNF antibodies are directed against TNF-alpha or TNF-beta. As disclosed in the specification, especially in Example 3, methods for generating, isolating, determining the titer of, and administering anti-TNF-alpha antibodies are disclosed. In addition, the specification, and the Examples set forth therein describe the administration of anti-TNF-alpha antibodies numerous times, including page 34, beginning at line 24 and page 37, beginning at line 20. Thus, the skilled artisan, when equipped with the present disclosure and the methods detailed therein, would readily understand that the methods detailed in Example 7 comprise the administration and use of anti-TNF-alpha antibodies.

The Examiner has also based the rejection of claims 42 and 46 under 35 U.S.C. §112, first paragraph on the ruling of *In re Fisher*, 1666 USPQ 19 at 24 (CCPA 1970), which indicates that the more unpredictable an area is, the more specific enablement must be in order to satisfy the statute. The Examiner has cited the Merck Manual of Medical Information (Merck Manual), pages 1018-1019 in order to argue that because the Merck Manual does not teach the administration of anti-cytokine antibodies for the treatment of AIDS, the recited combination of antibodies is unpredictable.

The Merck Manual does not lead to the conclusion that the present invention is unpredictable, and thus not enabled. The Examiner states that because the Merck Manual discloses that AIDS is treated with reverse transcriptase inhibitors and protease inhibitors, the methods of the present invention are unpredictable. Applicants respectfully argue that the drug regimens disclosed in the Merck Manual do not render the claimed invention unpredictable, but merely serve to emphasize the novelty of Applicants' invention, as it is not described in an art-accepted general reference. The fact that the Merck Manual does not teach the treatment of AIDS with a combination of antibodies to IFN gamma, TNF alpha, and IFN alpha only demonstrates that the present invention is new, and does nothing to lend credence to the argument that the instant invention is unpredictable.

Moreover, the Merck Manual does not purport to present an exhaustive list of the methods and compositions used to treat AIDS. As written in the section entitled "Treatment" on page 1018 of the Merck Manual, "Many drugs are now available to treat HIV infection, including the nucleoside reverse transcriptase inhibitors...". Therefore, the Examiner's assertion

that because anti-cytokine antibodies are not listed in the Merck Manual, the instant invention is unpredictable does not stand. The list of drugs in the Merck Manual is merely illustrative, and the section cited by the Examiner does not purport to be the definitive resource for every therapy available for treating AIDS.

The Examiner also contends that the specification does not provide sufficient guidance to extrapolate the successful treatment of rheumatoid arthritis and ankylosing spondylitis to the treatment of AIDS, and the mechanism of autoimmune diseases is diverse and incompletely understood, and therefore the claimed invention is unpredictable and the experimentation for one of skill in the art is improperly extensive and undue. The Examiner cites the specification at page 40, last paragraph, and page 41, lines 10-18, where the specification discloses that a common mechanism underlies all autoimmune diseases.

Applicants respectfully argue that, as amply demonstrated by the specification, autoimmune diseases with diverse clinical profiles are successfully treated by the methods of the present invention. Ankylosing spondylitis and rheumatoid arthritis manifest in different locations (the back and neck versus the extremities and internal organs, respectively), different parts of the body are attacked (bone versus joints and organs, respectively), and uncontrolled disease results in different outcomes (fusion of the vertebrae versus permanent disability). While these diseases differ considerably in virtually every aspect, they are amenable to the same treatment. Further, as disclosed in the instant specification, particularly at page 3, beginning at line 1, the autoimmune component of AIDS and the multiple similarities between AIDS and other autoimmune diseases, especially regarding cytokine expression, has been expounded upon in numerous teachings. Thus, the skilled artisan, armed with the present disclosure and the knowledge of the autoimmune component of AIDS can readily practice the methods of the present invention with predictable results.

The Examiner's also argues that the experimentation left to those of skill in the art is unnecessarily and improperly undue and extensive. The Examiner bases this assertion on the holding of *Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd.*, 927 F.2d 1200 (Fed. Cir. 1991). Applicants note that the facts of *Amgen* and the instant claims are significantly distinct, and the opinion is narrowly tailored to broad claims to DNA sequences. Moreover, the court in *Amgen* stated that, "...it is not necessary that a patent applicant test all the embodiments of his invention, *In re Angstadt*, 537 F.2d 498, 502, 190 USPQ 214, 218 (CCPA 1976); what is necessary is that

he provide a disclosure sufficient to enable one of skill in the art to carry out the invention commensurate with the scope of his claims.” Applicants respectfully submit that they have met all of the criteria set forth by the court in *Amgen*, and the skilled artisan would not be required to engage in undue experimentation in order to practice the methods of the present invention. One of skill in the art, when armed with the present disclosure, would know how to make an antibody to interferon gamma, interferon alpha, and tumor necrosis factor alpha (e.g. page 21, beginning at line 24, page 34 beginning at line 5). One of skill in the art, when armed with the present disclosure, would know how to administer an antibody to interferon gamma, interferon alpha, and tumor necrosis factor alpha to a patient in need thereof (e.g. page 26, beginning at line 18, page 34, beginning at line 15). One of skill in the art, when armed with the present disclosure, would know that the administration of anti-cytokine antibodies results in a detectable improvement in an AIDS patient’s health (e.g. page 40, beginning at line 18). One of skill in the art, when armed with the present disclosure, would know that the administration of anti-interferon alpha antibodies results in a clinical improvement in AIDS patients (e.g. page 40, beginning at line 18), and that increased levels of the inflammatory cytokines tumor necrosis factor alpha and interferon gamma are closely related to the clinical progression of AIDS (e.g. page 3, beginning at line 28). Thus, the instant specification adequately discloses to the skilled artisan how to carry out the invention commensurate with the scope of the instant claims. No undue experimentation is necessary.

The Examiner has also rejected claims 42 and 46 under 35 U.S.C. §112, first paragraph, on the belief that the recited term “biologically active fragment” requires an undue amount of experimentation in order to predict which biologically active fragments of an antibody would be effective in the recited method.

Applicants respectfully submit that the specification is enabling for a method of treating AIDS in a patient comprising administering, *inter alia*, biologically active fragments of antibodies. That is, e.g., page 21, commencing at line 1 of the specification, sets forth, “The term “biologically active fragment” is intended to mean a part of the complete molecule which retains all or some of the catalytic or biological activity possessed by the complete molecule, especially activity that allows specific binding of the antibody to an antigenic determinant”. Thus the skilled artisan, when equipped with the present specification and the disclosure therein, would readily understand that a biologically active fragment comprises a molecule that binds to a

cytokine, including interferon gamma, tumor necrosis factor alpha, interferon alpha, or any other antigenic determinant encompassed by the present invention.

However, without wishing to acquiesce to the Examiner's construction, but rather in an attempt to expedite the prosecution of this application, Applicants have amended claim 46 to recite monoclonal antibodies, polyclonal antibodies, combinations thereof, biologically active wherein the biologically active fragment is a fragment of an antibody that binds gamma interferon, tumor necrosis factor alpha, or interferon alpha, and allelic or species variants thereof.

Support for the present amendments can be found throughout the specification as filed. For example, at page 12, beginning at line 3, where molecules and antibodies that bind, neutralize or inhibit cytokines are described. Further, at page 15, beginning at line 19, molecules and antibodies that bind, inhibit, or neutralize various compounds, including hyperproduced cytokines such as interferon gamma, tumor necrosis factor alpha or interferon alpha are described. Additionally, at page 22, beginning at line 16, biologically active fragments of antibodies comprising the specific activity of binding an antigenic determinant, such as a cytokine like interferon gamma, tumor necrosis factor alpha or interferon alpha are described. Moreover, at page 20, commencing at line 1, autoimmune inhibitors, including biologically active fragments of antibodies that bind, inhibit or neutralize or inhibit the autoimmunogen involved with the clinical manifestation of the autoimmune disease in the patient are described. In addition, Fab fragments of antibodies are described on page 23, beginning at line 5. Therefore, the present amendment does not add new matter, and is fully supported by the specification.

Applicants respectfully request that the Examiner's rejection pursuant to 35 U.S.C. §112, first paragraph is reconsidered and withdrawn.

Summary

Applicants respectfully submit that each rejection of the Examiner to the claims of the present application has been overcome or is now inapplicable, and that claims 42 and 46 are now in condition for allowance. Applicants further submit that no new matter has been added by way of the present amendment. Reconsideration and allowance of these claims is respectfully requested at the earliest possible date.

Respectfully submitted,

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